Tuning microenvironment modulus and biochemical composition promotes human mesenchymal stem cell tenogenic differentiation.

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Public Summary:
Mesenchymal stem cells (MSCs) are promising for the regeneration of tendon and ligament tissues. In order for MSCs to differentiate to tendon tissue, they require appropriate environmental cues. Here, we utilized a mathematical design of experiments to examine the effects that different combinations of environmental stimuli have on MSC differentiation into tendon and ligament tissues. Specifically, we used different chemistries to make 3D culture systems that differed in stiffness and ratios of incorporated MSC-binding molecules. We found that MSCs tenogenic/ligamentogenic gene expression was altered in response to stiffness of the 3D culture system as well as other contact cues that were incorporated into the 3D culture. These findings could inform the design of materials for tendon/ligament regeneration.

Scientific Abstract:
Mesenchymal stem cells (MSCs) are promising for the regeneration of tendon and ligament tissues. Toward realizing this potential, microenvironment conditions are needed for promoting robust lineage-specific differentiation into tenocytes/ligament fibroblasts. Here, we utilized a statistical design of experiments approach to examine combinations of matrix modulus, composition, and soluble factors in human MSC tenogenic/ligamentogenic differentiation. Specifically, well-defined poly(ethylene glycol)-based hydrogels were synthesized using thiol-ene chemistry providing a bioinert base for probing cell response to extracellular matrix cues. Monomer concentrations were varied to achieve a range of matrix moduli (E approximately 10-90 kPa), and different ratios of integrin-binding peptides were incorporated (GFOGER and RGDS for collagen and fibronectin, respectively), mimicking aspects of developing tendon/ligament tissue. A face-centered central composite response surface design was utilized to understand the contributions of these cues to human MSC differentiation in the presence of soluble factors identified to promote tenogenesis/ligamentogenesis (BMP-13 and ascorbic acid). Increasing modulus and collagen mimetic peptide content increased relevant gene expression and protein production or retention (scleraxis, collagen I, tenascin-C). These findings could inform the design of materials for tendon/ligament regeneration. More broadly, the design of experiments enabled efficient data acquisition and analysis, requiring fewer replicates than if each factor had been varied one at a time. This approach can be combined with other stimuli (for example, mechanical stimulation) toward a better mechanistic understanding of differentiation down these challenging lineages. (c) 2016 Wiley Periodicals, Inc. J Biomed Mater Res Part A: 104A: 1162-1174, 2016.